Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan (CCX168) in Patients with C3 Glomerulopathy

Summary

EudraCT number	2017-001821-42
Trial protocol	GB BE DE NL ES DK FR IT IE
Global end of trial date	27 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	CL011_168

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 132 321

Notes:

Sponsors

Sponsor organisation name	ChemoCentryx, Inc.
Sponsor organisation address	850 Maude Avenue, Mountain View, California, United States, 94043
Public contact	Clinical trial disclosure, ChemoCentryx, Inc., +1 650 210 2900, clinicaltrials@chemocentryx.com
Scientific contact	Clinical trial disclosure, ChemoCentryx, Inc., +1 650 210 2900, clinicaltrials@chemocentryx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2021
Global end of trial reached?	Yes
Global end of trial date	27 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of avacopan compared to placebo based on histologic changes in kidney biopsies taken before and during treatment.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulations of the locale and country where the study was conducted, and in compliance with Good Clinical Practice Guidelines. Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. The rationale of the study, procedural details, and investigational goals were explained to each subject, along with potential risks and benefits. Each subject was assured of his/her right to withdraw from the study at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ireland: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	57
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	51
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 104 subjects screened.

Period 1

Period 1 title	Blinded treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Group

Arm description:

Avacopan matching placebo
Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population.
ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population.

Arm type	Placebo
Investigational medicinal product name	Avacopan Matching Placebo
Investigational medicinal product code	
Other name	Placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules x 3 administered twice daily during the 26-week blinded treatment period

Arm title	Avacopan Group

Arm description:

Avacopan (formerly CCX168)
Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population.
ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population

Arm type	Experimental
Investigational medicinal product name	Avacopan
Investigational medicinal product code	
Other name	CCX168
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Avacopan (formerly CCX168) 10 mg capsules x 3 administered twice daily during the blinded 26-week blinded treatment period

Number of subjects in period 1	Placebo Group	Avacopan Group
Started	29	28
Completed	25	22
Not completed	4	6
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	2
Other	2	1
Investigator Decision	1	-
Sponsor decision	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Group
Reporting group description:	
Avacopan matching placebo Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population. ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population.	
Reporting group title	Avacopan Group
Reporting group description:	
Avacopan (formerly CCX168) Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population. ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population	

Reporting group values	Placebo Group	Avacopan Group	Total
Number of subjects	29	28	57
Age categorical Units: Subjects			
12-17 years	2	0	2
18-50 years	20	23	43
51-65 years	4	4	8
>65 years	3	1	4
Age continuous Units: years			
arithmetic mean	37.2	32.2	
standard deviation	± 17.53	± 15.03	-
Gender categorical Units: Subjects			
Female	13	9	22
Male	16	19	35
Ethnicity Units: Subjects			
Hispanic or Latino	4	2	6
Not Hispanic or Latino	25	26	51
Race Units: Subjects			
Asian	3	2	5
Black or African American	0	1	1
White	25	24	49
Unknown or Not Reported	1	1	2
Region of Enrollment Units: Subjects			
Canada	2	3	5
Netherlands	5	1	6
Belgium	1	2	3

United States	10	11	21
Ireland	3	3	6
Denmark	1	1	2
Italy	1	0	1
United Kingdom	2	2	4
Germany	2	1	3
Spain	2	4	6
Geographic Region Units: Subjects			
North America	12	14	26
Rest of World	17	14	31
C3GN or DDD			
C3GN=C3 Glomerulonephritis; DDD=Dense Deposit Missing refers to one subject for whom disease type (C3GN vs DDD) could not be determined and subject was randomized in error.			
Units: Subjects			
C3GN	25	23	48
DDD	4	4	8
Missing	0	1	1
History of Kidney Transplant			
Missing refers to one subject for whom disease type (C3GN vs DDD) could not be determined and subject was randomized in error.			
Units: Subjects			
Yes	2	1	3
No	27	26	53
Missing	0	1	1
C5b-9 Stratum			
C5b-9 levels <= 244 ng/mL were normal according to the central laboratory used for the study. Defined by assay normal range.			
Units: Subjects			
> 244 ng/mL	22	21	43
<= 244 ng/mL	7	7	14
UPCR (g/g)			
UPCR=Urine Protein to Creatinine Ratio Urine protein-to-creatinine ratio (UPCR): UPCR was calculated by dividing the level of protein in a spot urine test by the creatinine level. UPCR estimates the 24-hour protein excretion in grams per day and is used in clinical practice and clinical trials to measure the severity of proteinuria in patients.			
Units: Subjects			
> 1 g/g	21	22	43
<= 1 g/g	8	6	14
Viral Test Results HIV-1/2 Antibody			
HIV=Human Immunodeficiency Virus			
Units: Subjects			
Reactive	0	0	0
Non-reactive	29	28	57
Viral Test Results - Hepatitis B Virus Surface Antigen Units: Subjects			
Reactive	0	0	0
Non-reactive	29	28	57
Viral Test Results - Hepatitis C Virus Antibody			

Units: Subjects			
Reactive	0	1	1
Non-reactive	29	27	56

Age at Diagnosis of C3G			
C3G=C3 Glomerulopathy			
Units: years			
arithmetic mean	33.3	28.2	
standard deviation	± 17.95	± 17.08	-
Duration of C3G			
Calculated from the time of first diagnosis based on renal biopsy. C3G=C3 glomerulopathy			
Units: months			
arithmetic mean	46.7	48.2	
standard deviation	± 43.78	± 46.38	-
eGFR			
eGFR=estimated Glomerular Filtration Rate			
Units: mL/ min/1.73m²			
arithmetic mean	72.34	79.29	
standard deviation	± 43.509	± 39.751	-
UPCR			
UPCR=Urine Protein to Creatinine Ratio Urine protein-to-creatinine ratio (UPCR): UPCR was calculated by dividing the level of protein in a spot urine test by the creatinine level. UPCR estimates the 24-hour protein excretion in grams per day and is used in clinical practice and clinical trials to measure the severity of proteinuria in patients.			
Units: g/g			
arithmetic mean	2.80	4.11	
standard deviation	± 2.435	± 3.380	-
Urinary MCP-1:Creatinine Ratio			
2 patients missed baseline Urinary MCP-1 data. Placebo group= 28 participants Avacopan group= 27 participants			
Units: pg/mg Creatinine			
arithmetic mean	750.29	1215.88	
standard deviation	± 492.542	± 1303.35	-
Body Weight			
Units: kilogram(s)			
arithmetic mean	72.65	78.33	
standard deviation	± 12.631	± 19.229	-
Height			
Units: centimetre(s)			
arithmetic mean	171.41	173.82	
standard deviation	± 8.773	± 10.805	-
BMI			
BMI=Body Mass Index			
Units: kilogram(s)/ square meter			
arithmetic mean	24.65	26.05	
standard deviation	± 3.410	± 6.375	-
EQ-5D-5L Index Score			
EQ-5D-5L=EuroQuality of Life-5 Domains-5 Levels The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems,			

moderate problems, severe problems and extreme problems. The answers given can be converted into an Index Score ranging from 0 for death to 1 for perfect health.			
Units: units on a scale			
arithmetic mean	0.88	0.87	
standard deviation	± 0.145	± 0.116	-
EQ-5D-5L VAS Score			
EQ-5D-5L=EuroQuality of Life-5 Domains-5 Levels VAS=Visual Analog Scale The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D questionnaire includes a Visual Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 (the worst imaginable health) to 100 (the best imaginable health).			
Units: units on a scale			
arithmetic mean	78.83	73.61	
standard deviation	± 20.604	± 19.070	-

End points

End points reporting groups

Reporting group title	Placebo Group

Reporting group description:

Avacopan matching placebo
Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population.
ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population.

Reporting group title	Avacopan Group

Reporting group description:

Avacopan (formerly CCX168)
Subjects with Elevated C5b-9 (> 244 ng/mL) and combined C5b-9 (elevated [> 244 ng/mL] and non-elevated C5b-9) in the ITT Population.
ITT Population: included all randomized subjects who received at least one dose of study medication; subjects with a histologic activity score of 0 at baseline or who were ongoing and had not completed the Week 26 visit were not included in the ITT population

Primary: Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Subjects With Elevated C5b-9

End point title	Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Subjects With Elevated C5b-9

End point description:

Change from baseline to Week 26 in the biopsy-based C3G Histologic Index for disease activity - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
C3G Histological Index for Disease Activity Scores can range from 0 to 21. A decrease indicates improvement.
C3G=C3 glomerulopathy

End point type	Primary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score on a scale				
least squares mean (confidence interval 95%)	-0.9 (-2.2 to 0.4)	-1.0 (-2.3 to 0.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical Analysis 1 for Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Subjects With Elevated C5b-9

Comparison groups	Placebo Group v Avacopan Group
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.967
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.8

Primary: Percent Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Combined C5b-9 Strata

End point title	Percent Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity - Combined C5b-9 Strata

End point description:

Percent change from baseline to Week 26 in the biopsy-based C3G Histologic Index for disease activity - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
C3G Histological Index for Disease Activity Scores can range from 0 to 21. A decrease indicates improvement.
C3G=C3 glomerulopathy
* Multiple Imputation: Missing Week 26 values are imputed using the regression method to create 100 complete datasets.

End point type	Primary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: Percentage change				
arithmetic mean (standard error)	26.20 (± 47.302)	-5.77 (± 5.904)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical Analysis 1 for Percent Change From Baseline to Week 26 in the C3G Histologic Index for Disease Activity -Combined C5b-9 Strata

Comparison groups	Avacopan Group v Placebo Group

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3083 [1]
Method	Van Elteren's Test
Parameter estimate	Mean difference (final values)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.83
upper limit	67.16

Notes:

[1] - Test for normality showed that mean change and mean percent change were not normally distributed. Van Elteren's test was then applied to test mean percent change.

Secondary: Proportion of Subjects Who Have a Histologic Response Defined as a Decrease (Improvement) in the Biopsy-based C3G Histologic Index for Activity of at Least 35% From Baseline to 26 Weeks - Subjects With Elevated C5b-9

End point title	Proportion of Subjects Who Have a Histologic Response Defined as a Decrease (Improvement) in the Biopsy-based C3G Histologic Index for Activity of at Least 35% From Baseline to 26 Weeks - Subjects With Elevated C5b-9

End point description:

Proportion of subjects who have a histologic response defined as a decrease (improvement) in the biopsy-based C3G Histologic Index for activity of at least 35% from baseline to 26 weeks - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
C3G Histological Index for Disease Activity Scores can range from 0 to 21. A decrease indicates improvement.
C3G=C3 glomerulopathy

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: Participants				
Responder	4	2		
Non-Responder	16	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Who Have a Histologic Response Defined as a

Decrease (Improvement) in the Biopsy-based C3G Histologic Index for Activity of at Least 35% From Baseline to 26 Weeks - Combined C5b-9 Strata

End point title	Proportion of Subjects Who Have a Histologic Response Defined as a Decrease (Improvement) in the Biopsy-based C3G Histologic Index for Activity of at Least 35% From Baseline to 26 Weeks - Combined C5b-9 Strata

End point description:

Proportion of subjects who have a histologic response defined as a decrease (improvement) in the biopsy-based C3G Histologic Index for activity of at least 35% from baseline to 26 weeks - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
C3G Histological Index for Disease Activity Scores can range from 0 to 21. A decrease indicates improvement.
C3G=C3 glomerulopathy

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Participants				
Responder	7	4		
Non-Responder	18	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in the C3G Histologic Index for Disease Chronicity - Subjects With Elevated C5b-9

End point title	Change From Baseline to Week 26 in the C3G Histologic Index for Disease Chronicity - Subjects With Elevated C5b-9

End point description:

Change from baseline to Week 26 in the biopsy-based C3G Histologic Index for disease chronicity over the placebo-controlled treatment period - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
C3G Histological Index for Disease Chronicity Scores can range from 0 to 10. A decrease indicates improvement.
C3G=C3 glomerulopathy

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	19		
Units: score on a scale				
least squares mean (confidence interval 95%)	1.5 (0.9 to 2.2)	1.1 (0.3 to 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 26 in the C3G Histologic Index for Disease Chronicity - Combined C5b-9 Strata

End point title	Change From Baseline to Week 26 in the C3G Histologic Index for Disease Chronicity - Combined C5b-9 Strata

End point description:

Change from baseline to Week 26 in the biopsy-based C3G Histologic Index for disease chronicity over the placebo-controlled treatment period - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
C3G Histological Index for Disease Chronicity Scores can range from 0 to 10. A decrease indicates improvement.
C3G=C3 glomerulopathy

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	26		
Units: score on a scale				
least squares mean (confidence interval 95%)	1.6 (1.1 to 2.2)	0.8 (0.2 to 1.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Assessed by Percent Change From Baseline Over 26 Weeks in eGFR - Subjects With Elevated C5b-9

End point title	Renal Function as Assessed by Percent Change From Baseline Over 26 Weeks in eGFR - Subjects With Elevated C5b-9

End point description:

The percent change from baseline over 26 weeks in estimated Glomerular Filtration Rate (eGFR) - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: Percentage change				
least squares mean (confidence interval 95%)	-4.73 (-12.29 to 2.83)	6.11 (-1.86 to 14.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Assessed by Percent Change From Baseline Over 26 Weeks in eGFR - Combined C5b-9 Strata

End point title	Renal Function as Assessed by Percent Change From Baseline Over 26 Weeks in eGFR - Combined C5b-9 Strata

End point description:

The percent change from baseline over 26 weeks in estimated Glomerular Filtration Rate (eGFR) - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Percentage change				
least squares mean (confidence interval 95%)	-5.88 (-12.32 to 0.56)	4.79 (-1.66 to 11.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Assessed by Change From Baseline Over 26 Weeks in eGFR - Subjects With Elevated C5b-9

End point title	Renal Function as Assessed by Change From Baseline Over 26 Weeks in eGFR - Subjects With Elevated C5b-9

End point description:

The change from baseline over 26 weeks in estimated Glomerular Filtration Rate (eGFR) - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: mL/min/1.73m²				
least squares mean (confidence interval 95%)	-3.57 (-8.43 to 1.29)	0.44 (-4.69 to 5.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Function as Assessed by Change From Baseline Over 26 Weeks in eGFR - Combined C5b-9 Strata

End point title	Renal Function as Assessed by Change From Baseline Over 26 Weeks in eGFR - Combined C5b-9 Strata

End point description:

The change from baseline over 26 weeks in estimated Glomerular Filtration Rate (eGFR) - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: mL/min/1.73m²				
least squares mean (confidence interval 95%)	-3.35 (-7.56 to 0.85)	0.47 (-3.75 to 4.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over 26 Weeks in UPCR in Patients With Abnormal UPCR at Baseline - Subjects With Elevated C5b-9

End point title	Percent Change From Baseline Over 26 Weeks in UPCR in Patients With Abnormal UPCR at Baseline - Subjects With Elevated C5b-9

End point description:

Percent change from baseline Over 26 Weeks in UPCR in patients with Abnormal UPCR at Baseline (>= 0.15 g/g) - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
LSM=Least Squares Mean; UPCR = Urine Protein:Creatinine Ratio

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: Percentage change				
least squares mean (confidence interval 95%)	-14 (-34 to 12)	-16 (-36 to 12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over 26 Weeks in UPCR in Patients With Abnormal UPCR at Baseline - Combined C5b-9 Strata

End point title	Percent Change From Baseline Over 26 Weeks in UPCR in Patients With Abnormal UPCR at Baseline - Combined C5b-9 Strata

End point description:

Percent change from baseline Over 26 Weeks in UPCR in patients with Abnormal UPCR at Baseline (>= 0.15 g/g) - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
LSM=Least Squares Mean; UPCR = Urine Protein: Creatinine Ratio

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: Percentage change				
least squares mean (confidence interval 95%)	-14 (-33 to 10)	-26 (-42 to -6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over 26 Weeks in Urinary MCP-1 - Subjects With Elevated C5b-9

End point title	Percent Change From Baseline Over 26 Weeks in Urinary MCP-1 - Subjects With Elevated C5b-9

End point description:

Percent change from baseline over 26 weeks in urinary MCP-1: creatinine ratio - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
LSM=Least Squares Mean; MCP-1=Monocyte Chemoattractant Protein-1

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: Percentage change				
least squares mean (confidence interval 95%)	1 (-18 to 25)	-23 (-39 to -4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline Over 26 Weeks in Urinary MCP-1 - Combined C5b-9 Strata

End point title	Percent Change From Baseline Over 26 Weeks in Urinary MCP-1 - Combined C5b-9 Strata

End point description:

Percent change from baseline over 26 weeks in urinary MCP-1: creatinine ratio - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
LSM=Least Squares Mean; MCP-1=Monocyte Chemoattractant Protein-1

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	23		
Units: Percentage change				
least squares mean (confidence interval 95%)	1 (-17 to 23)	-12 (-28 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over 26 Weeks in EQ-5D-5L Health Scale VAS and Index Score - Subjects With Elevated C5b-9

End point title	Change From Baseline Over 26 Weeks in EQ-5D-5L Health Scale VAS and Index Score - Subjects With Elevated C5b-9

End point description:

Change from baseline over 26 weeks in EQ-5D-5L Health Scale VAS and Index Score - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
EQ-5D-5L: EuroQuality of Life-5 Domains-5 Levels.
The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The answers given can be converted into an Index Score ranging from 0 for death to 1 for perfect health. The EQ-5D questionnaire also includes a Visual Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 (the worst imaginable health) to 100 (the best imaginable health).

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: score on a scale				
least squares mean (confidence interval 95%)				
EQ-5D-5L VAS Score	-3.5 (-7.8 to 0.8)	-1.9 (-6.4 to 2.7)		
EQ-5D-5L Index Score	0.0220 (-0.0206 to 0.0647)	-0.0202 (-0.0653 to 0.0249)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over 26 Weeks in EQ-5D-5L Health Scale VAS and Index Score - Combined C5b-9 Strata

End point title	Change From Baseline Over 26 Weeks in EQ-5D-5L Health Scale VAS and Index Score - Combined C5b-9 Strata

End point description:

Change from baseline over 26 weeks in EQ-5D-5L Health Scale VAS and Index Score - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
EQ-5D-5L: EuroQuality of Life-5 Domains-5 Levels.
The EQ-5D-5L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The answers given can be converted into an Index Score ranging from 0 for death to 1 for perfect health. The EQ-5D questionnaire also includes a Visual Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 (the worst imaginable health) to 100 (the best imaginable health).

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: score on a scale				
least squares mean (confidence interval 95%)				
EQ-5D-5L VAS Score	0.1 (-3.9 to 4.2)	-1.9 (-6.0 to 2.2)		
EQ-5D-5L Index Score	0.0060 (-0.0334 to 0.0454)	-0.0138 (-0.0533 to 0.0256)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over 26 Weeks in SF-36 v2 - Subjects With Elevated C5b-9

End point title	Change From Baseline Over 26 Weeks in SF-36 v2 - Subjects With Elevated C5b-9

End point description:

Change from baseline over 26 weeks in SF-36 v2 - Subjects with Elevated C5b-9 (> 244 ng/mL) in the Intent-to-Treat Population.
SF-36v2: Medical Outcomes Survey Short Form-36 version 2.
SF-36v2 measures each of the following eight health domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Scores on each item are summed and averaged. The SF-36v2 component domain scores range from 0 (worst health) to 100 (best health)

End point type	Secondary

End point timeframe:

Week 26

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[2]	19[3]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
SF-36v2: Physical Functioning	2.8518 (-3.2409 to 8.9446)	3.2197 (-3.3108 to 9.7502)		
SF-36v2: Role-Physical	-4.2592 (-11.5984 to 3.0801)	3.5162 (-4.2634 to 11.2958)		
SF-36v2: Bodily Pain	3.6 (-4.2 to 11.4)	-3.5 (-12.0 to 4.9)		
SF-36v2: General Health Perceptions	-0.9 (-7.0 to 5.2)	1.6 (-4.8 to 8.0)		
SF-36v2: Vitality	-2.472 (-8.906 to 3.963)	3.898 (-2.978 to 10.774)		
SF-36v2: Social Functioning	4.58 (-2.30 to 11.47)	0.34 (-7.20 to 7.88)		
SF-36v2: Role-Emotional	0.6859 (-6.8507 to 8.2225)	3.2461 (-4.6899 to 11.1821)		
SF-36v2: Mental Health	2.423 (-3.684 to 8.530)	2.730 (-3.791 to 9.251)		
SF-36v2: Mental Component	0.7556 (-2.3560 to 3.8672)	0.7608 (-2.6341 to 4.1558)		
SF-36v2: Physical Component	-0.3257 (-2.6090 to 1.9576)	0.0762 (-2.4423 to 2.5947)		

Notes:

[2] - All categories have 20 participants except SF-36v2: General Health Perceptions with 19.

[3] - All categories have 18 participants except SF-36v2: Bodily Pain and Social Functioning with 17.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over 26 Weeks in SF-36 v2 - Combined C5b-9 Strata

End point title	Change From Baseline Over 26 Weeks in SF-36 v2 - Combined C5b-9 Strata

End point description:

Change from baseline over 26 weeks in SF-36 v2 - Combined C5b-9 Strata (elevated [> 244 ng/mL] and non-elevated C5b-9) in the Intent-to-Treat Population.
SF-36v2: Medical Outcomes Survey Short Form-36 version 2.
SF-36v2 measures each of the following eight health domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Scores on each item are summed and averaged.

The SF-36v2 component domain scores range from 0 (worst health) to 100 (best health).

End point type	Secondary
End point timeframe:	
Week 26	

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[4]	26[5]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
SF-36v2: Physical Functioning	2.9619 (-2.7150 to 8.6389)	4.6532 (-1.1123 to 10.4187)		
SF-36v2: Role-Physical	-2.4712 (-9.6179 to 4.6755)	1.2077 (-5.9734 to 8.3887)		
SF-36v2: Bodily Pain	1.5 (-5.7 to 8.7)	-2.0 (-9.3 to 5.4)		
SF-36v2: General Health Perceptions	-1.0 (-6.6 to 4.6)	0.7 (-4.9 to 6.2)		
SF-36v2: Vitality	-0.468 (-6.283 to 5.348)	4.085 (-1.782 to 9.952)		
SF-36v2: Social Functioning	4.66 (-1.41 to 10.73)	1.55 (-4.66 to 7.76)		
SF-36v2: Role-Emotional	4.3024 (-3.3147 to 11.9195)	7.8375 (0.2129 to 15.4620)		
SF-36v2: Mental Health	1.503 (-3.911 to 6.917)	3.914 (-1.543 to 9.370)		
SF-36v2: Mental Component	1.3591 (-1.7970 to 4.5153)	2.3874 (-0.8529 to 5.6277)		
SF-36v2: Physical Component	-0.3578 (-2.5452 to 1.8296)	-0.5096 (-2.7680 to 1.7489)		

Notes:

[4] - All categories have 25 participants except SF-36v2: General Health Perceptions with 24 participants

[5] - All categories have 25 participants except SF-36v2: Bodily Pain and Social Functioning with 24.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent SAEs, AEs, Relatedness to Study Medication and Withdrawals Due to AEs

End point title	Number of Subjects With Treatment-emergent SAEs, AEs, Relatedness to Study Medication and Withdrawals Due to AEs

End point description:

Number of Subjects with Treatment-emergent SAEs, AEs, relatedness to study medication and Withdrawals Due to AEs
AEs=Adverse events SAEs=Serious adverse events TEAE=Treatment-emergent adverse events
'Possibly related' refers to the Investigators' causality assessment

Safety Population: The safety population included all subjects who were randomized and had received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 182/week 26)

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: Participants				
Number of subjects with at least one TEAE	24	25		
Number of subjects with SAEs	3	3		
Subjects with TEAEs related to Study Medication	11	10		
Subjects with TEAEs leading to discontinuation	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment-emergent SAEs, AEs, Relatedness to Study Medication and Withdrawals Due to AEs

End point title	Number of Treatment-emergent SAEs, AEs, Relatedness to Study Medication and Withdrawals Due to AEs

End point description:

Number of Treatment-emergent SAEs, AEs, relatedness to study medication and Withdrawals Due to AEs
AEs=Adverse events SAEs=Serious adverse events TEAE=Treatment-emergent adverse events
'Possibly related' refers to the Investigators' causality assessment
Safety Population: The safety population included all subjects who were randomized and had received at least one dose of study drug.

End point type	Secondary

End point timeframe:

From day 1 throughout the study period (day 182/week 26)

End point values	Placebo Group	Avacopan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: Participants				
Number of TEAEs	107	149		
Number of SAEs	4	6		
TEAEs possibly related to Study Medication	24	38		

Number of TEAEs leading to discontinuation	2	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From day 1 throughout the study period (day 182/week 26)

Adverse event reporting additional description:

An adverse event is considered treatment-emergent if the start date/time of the event is on or after the date/ time of first study drug treatment up to the final observation in the double-blind treatment period (week 26).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo Group

Reporting group description:

Avacopan-matching placebo capsules x 3 administered twice daily during the 26 week blinded treatment period
Avacopan-matching placebo: Orally administered
The safety population included all subjects who were randomized and had received at least one dose of study drug.

Reporting group title	Avacopan Group

Reporting group description:

Avacopan (formerly CCX168) 10 mg capsules x 3 administered twice daily during the blinded 26 week blinded treatment period
Avacopan: Orally administered
The safety population included all subjects who were randomized and had received at least one dose of study drug.

Serious adverse events	Placebo Group	Avacopan Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 29 (10.34%)	3 / 28 (10.71%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Sjogren's syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial parotitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo Group	Avacopan Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 29 (82.76%)	25 / 28 (89.29%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 29 (10.34%)	3 / 28 (10.71%)	
occurrences (all)	3	4	
Orthostatic hypotension			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	1 / 29 (3.45%)	5 / 28 (17.86%)	
occurrences (all)	1	6	
Pyrexia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 29 (3.45%)	3 / 28 (10.71%)	
occurrences (all)	1	4	
Blood creatine increased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 29 (6.90%)	5 / 28 (17.86%)	
occurrences (all)	4	5	
Tremor			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 29 (10.34%)	3 / 28 (10.71%)	
occurrences (all)	3	3	
Lymphopenia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)	2 / 28 (7.14%)	
occurrences (all)	4	2	

Dyspepsia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Mouth ulceration			
subjects affected / exposed	2 / 29 (6.90%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	4 / 28 (14.29%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	3	1	
Muscle spasms			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Pain in extremity			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Lower respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	3 / 29 (10.34%)	1 / 28 (3.57%)	
occurrences (all)	4	1	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	2 / 28 (7.14%) 3	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	3 / 28 (10.71%) 3	
Hyperkalaemia subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	1 / 28 (3.57%) 2	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 28 (7.14%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2017	Protocol amendment 1 • added 12-lead ECG to screening and safety assessments • added urinary albumin:creatinine ratio (UACR) and protein: creatinine ratio (UPCR) to screening evaluations • clarified that the week 52 biopsy in adolescent subjects was optional and was not a protocol deviation if not collected • added active uncontrolled infection to the exclusion criteria • clarified that pharmacodynamic markers were exploratory endpoints • clarified albuminuria measurement • clarified that it was not necessary to use CTCAE grading for clinical events. CTCAE criteria could be used for severity assessment of lab values. If there was a clinical adverse event related to a lab abnormality, the adverse event was to be reported as the clinical event, where possible. • added a new section to accommodate reports of overdose, misuse and abuse of the investigational medicinal product. All associated adverse events were to be reported as adverse events or serious adverse events using the adverse events electronic case report form (eCRF) and/or the serious adverse event report form. • added instruction that subjects who terminated early from the trial would have serious adverse events recorded at follow-up visits or at least 30 days after last investigational product administration. • added instruction that serious adverse event information should be entered as soon as possible when EDC access is returned.

16 April 2018	Protocol Amendment 2 • added a secondary population with diagnosed C3G and lower levels of circulating C5b-9 levels which was previously excluded • expanded screening from 4 weeks to 6 weeks • clarified that adolescent subjects were enrolled only in regulatory territories where approval was received, and that the dose in adolescents depended on body weight and avacopan plasma exposure (AUC0-6hr) or avacopan trough concentrations • expanded the number of subjects enrolled in the study from 44 to 88 • added to inclusion criteria that the Investigator would provide assurance that adolescent subjects were willing and able to ingest the size "0" tablet • clarified that CT-scan or chest X-ray was not mandatory, if evidence of tuberculosis was excluded by other methods described • increase the number of lesions to be included in the C3G Histologic Index for disease activity from 4 to 7 • expanded description of the C3G Histologic Index for Activity scoring system using the glomerulopathy histologic score as described by Bomback et al (Bomback et al, 2018) • added text to the statistics methods to accommodate the new C5b-9 strata • added that missing data would be imputed with the last observation carried forward (LOCF). Multiple imputation using other statistical methods could also be performed. • added that the day 183 morning dose for adolescent subjects was to be taken in the clinic rather than at home • added that subjects were to be reminded through a telephone call that the week 52 dose should not be taken. • added that the final 4 PK samples (Weeks 52, 54, 57, 60) were for terminal PK evaluation • added exploratory endpoints around PK parameters and PK/PD relationship • added criteria for potential for early termination of the stratum with C5b 9 levels 244 ng/m • added that PK parameters would be calculated based on plasma concentration for samples collected on both day 1 and day 183 (week 26)
02 August 2018	Protocol Amendment 3 • added visits at week 23, 35, 41, and 48 per DMC recommendation to increase the frequency of liver testing; data on concomitant medications and Adverse events were to be collected for the added visits • added serum chemistries at week 2, 23, 35, 41, and 48 per DMC recommendation to increase the frequency of liver testing • added that any changes in concomitant medication use were to be recorded per DMC recommendation • added new safety information from an ongoing clinical trial in a different indication to coincide with updated Reference Safety Information in the Investigator's Brochure • clarified that a follow-up renal biopsy was to be performed within 2 weeks before the week 26 visit and was to be completed before open-label medication was started • added scale to be used for crescent formation and fibrinoid necrosis involvement • clarified hepatic enzyme criteria under which dosing with investigational product would be suspended for that subject during investigation into the causality of abnormal liver tests and criteria for resumption of investigational product.

20 March 2019	Protocol Amendment 4 • clarified throughout that the investigational product was blinded • increased the duration of the study from 26 to 32 months to accommodate previous increase in sample size and slower than expected enrollment • updated the earliest time point for primary efficacy analysis • increase the frequency of hematology testing per DMC recommendation • clarified time allowed to differentiate between common fluctuations of renal function and true deterioration of renal function to prevent unnecessary discontinuation • clarified that investigational product dosing was paused during investigation of causality of abnormal liver tests, abnormal hematology, and serum chemistry tests and investigational product was to be discontinued, if applicable • updated clinical evaluation to include current clinical status, clarify patient safety information and to include the clinical safety information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 April 2020	Paused screening due to COVID-19	25 June 2020
02 October 2020	Paused screening to any new participants with analysis of efficacy data and sent confirmation to sites on 12-Feb-2021 following the results of the analysis, no further subjects would be enrolled.	-

Notes:

Limitations and caveats

None reported